PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MARK FRIDMAN
7 JABOTINSKY ST.
RAMAT GAN, ISRAEL 52520

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing (*day/month/year*) 27 NOV 2006
Applicant's or agent's file reference 1054/7	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date (*day/month/year*)
PCT/IL05/00369	03 April 2005 (03.04.2005)	04 April 2004 (04.04.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC: **A61B 5/08**(2006.01),7/00(2006.01)
USPC: 600/529,586

Applicant

BEN GURION UNIVERSITY OF THE NEGEV RESEARCH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	02 November 2006 (02.11.2006)	Navin Natnithithadha Telephone No. (571) 272-2975

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL05/00369

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL05/00369

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 27-29	YES
	Claims 1-26 and 30-33	NO
Inventive step (IS)	Claims 27-29	YES
	Claims 1-26 and 30-33	NO
Industrial applicability (IA)	Claims 1-33	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1-26 and 30-33 lack novelty under PCT Article 33(2) as being anticipated by Gavriely, US 6,168,568 B1 ("D1").

D1 teaches a device and method of detecting a one lung ventilation situation (see fig. 1), comprising: using a plurality of acoustic sensors 4, which are disposed on the body, to electronically detect lung sounds; and using a processing unit 20 to generate an output indicative of the one lung ventilation situation (see col. 19, ll. 35-51). The dependent claims are not novel over the disclosure of D1.

Claims 27-29 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a method comprising: identifying a one lung intubation situation in subpopulation of a selected population of human subjects, and the following:
(i) wherein at most 9.6% of the identifications are misidentifications; (ii) wherein at most 4.8% of the identifications are false positive identifications, and at most 4.8% of the identifications are false negative identifications; or
(iii) wherein at most 9% of the identifications are false positive identifications, and at most 2% of the identifications are false negative identifications.

Claims 1-33 meet the criteria set out in PCT Article 33(4), and thus meeting industrial applicability because the subject matter claimed can be made or used in industry.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

FRIEDMAN, Mark
7 Jabotinsky St.
52520 Ramat Gan
ISRAËL

Date of mailing *(day/month/year)* 06 December 2006 (06.12.2006)	
Applicant's or agent's file reference 1054/7	IMPORTANT NOTIFICATION
International application No. PCT/IL2005/000369	International filing date *(day/month/year)* 03 April 2005 (03.04.2005)
International publication date *(day/month/year)* 13 October 2005 (13.10.2005)	Priority date *(day/month/year)* 04 April 2004 (04.04.2004)
Applicant BEN GURION UNIVERSITY OF THE NEGEV RESEARCH AND DEVELOPMENT AUTHORITY et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)***An asterisk (*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
04 April 2004 (04.04.2004)	60/559,993	US	17 November 2006 (17.11.2006) *

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10/599598

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/IL2005/000369

International filing date: 03 April 2005 (03.04.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/559,993
Filing date: 04 April 2004 (04.04.2004)

Date of receipt at the International Bureau: 17 November 2006 (17.11.2006)

Remark: Priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

PA 1523872

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

October 03, 2006

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: *60/559,993*
FILING DATE: *April 04, 2004*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US60/559,993*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

L. Edelen

L. EDELEN
Certifying Officer

PTO/SB/16 (01-04)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

Express Mail Label No. 040473999

INVENTOR(S)		
Given Name (first and middle (if any))	Family Name or Surname	Residence (City and either State or Foreign Country)
Amon	COHEN	ISRAEL

Additional inventors are being named on the _____ separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

Continuous Monitoring of Separate Lung Ventilation

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☐ Customer Number. _____

OR

☐ Firm or Individual Name	Prof. Amon COHEN				
Address	ROTEM st. 47				
Address					
City	OMER	State		Zip	84965
Country	ISRAEL	Telephone	972-53-401064		

ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 3 ☐ CD(s), Number _____

☐ Drawing(s) *Number of Sheets* _____ ☐ Other (specify) _____

☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☑ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees.

☐ The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number _____

☑ Payment by credit card. Form PTO-2038 is attached.

FILING FEE Amount ($)
80 USD

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE Arnon Cohen

TYPED or PRINTED NAME Prof. Arnon Cohen

TELEPHONE 00-972-53-401064

Date April 1st 2004

REGISTRATION NO. _____ *(if appropriate)*

Docket Number _____

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2

PROVISIONAL APPLICATION COVER SHEET
Additional Page

PTO/SB/16 (08-03)
Approved for use through 07/31/2003. OMB 0651-0032
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Docket Number	

INVENTOR(S)/APPLICANT(S)		
Given Name (first and middle (if any)	Family or Surname	Residence (City and either State or Foreign Country)
Gabriel M.	GURMAN	ISRAEL

Number 1 of 1

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

Provisional Patent Application of:

COHEN Arnon and GURMAN Gabriel M.

CONTINUOUS MONITORING OF SEPARATE LUNG VENTILATION

Endobronchial intubation (intubation of a main bronchus) or one lung intubation (OLI) is a major incident during endotracheal (ET) intubation for general anesthesia or mechanical ventilation in the intensive care units (ICU). The ventilated lung (usually the right), suffers from hyperinflation, barotrauma and higher incidence of pneumothorax, while the non-ventilated lung becomes non-aerated and collapsed. Since the blood supply to the collapsed lung is reduced, but not completely discontinued, a significant reduction of body oxygenation follows and a gradual rise in blood partial pressure of CO_2 may happen. Symptoms which follow OLI are rising ventilation pressures, oxygen desaturation, changes in ET CO_2 and tachycardia. Unfortunately they show up rather late, sometimes after the lung injury was already produced.

As per today instrumental methods used for early diagnosis of OLI- lung auscultation, pulse oxymetry and capnography- have all been found to be non specific and controversial and all allert only after the symptoms have already been developed.

We have developed a system which can detect OLI based on electronic detection of ventilated lung sounds during artificial ventilation, manual or mechanical. Using several (usually four) piezoelectric microphones (or other sensors such as accelerometers and others) placed on the patient (usually but not necessarily on the back) during anesthesia, we use several algorithms which analyze the breathing sounds and identify that lung which is significantly less or not at all ventilated.

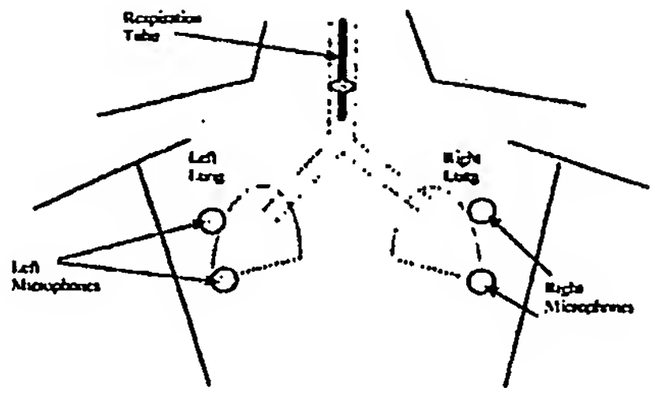

Fig. 1: microphone placement on the patient.

One of the algorithms used is based on the estimation of number of sources triggering the sensor array system. One of the simpler versions of this algorithm is based on an Auto-Regressive model that describes the dynamic MIMO (Multi Input Multi Output) system of acoustic transmission and absorption between the multi acoustic sources (Lungs, heart, muscles and noise) and the sensors array. This model can analyze the detected sources and discriminate among lungs and other sources thus able to determine OLI.

The goal of this algorithm is to estimate the number of sources from the signals that is received by the sensors. Let K and L, denote the number of sources (lungs) and sensors (microphones), respectively ($K<L$). The relation between the source signals and the measurements is give by a MIMO (Multi Input Multi Output) AR model:

$$\mathbf{y}[n] = \mathbf{A}\mathbf{u}[n] + \mathbf{C}\mathbf{x}[n] + \mathbf{e}[n],$$

$\mathbf{A}$ is $L \times ML$ matrix, where $\mathbf{a}_{ij}$, is an $M \times 1$ vector, $\mathbf{C}$ is $L \times K$ matrix whose elements, c_{ij}, relates the sensor i with the source j and finally, $\mathbf{e}[n]$ is $L \times 1$ vector that represents an additive white Gaussian noise. We assume that the sources and noise signals are independent, zero mean, Gaussian with covariance matrices $\mathbf{I}$ and $\sigma^2\mathbf{I}$ respectively. The conditional distribution of $\mathbf{y}[n]/\mathbf{u}[n]$ is Gaussian: $\mathbf{y}[n]/\mathbf{u}[n] \sim N(\mathbf{A}\mathbf{u}[n], \mathbf{R})$,
where $\mathbf{R} = \mathbf{C}\mathbf{C}^T + \sigma^2\mathbf{I}$.

In order to determine the number of sources (lungs), K, the algorithm first estimates the unknown matrices, $\mathbf{A}$ and $\mathbf{R}$, from the N samples of the data: $\mathbf{y}[1],\ldots,\mathbf{y}[N]$.

For this purpose, the Maximum–Likelihood (ML) estimator is used. The ML estimator of the matrices $\mathbf{A}$ and $\mathbf{R}$, is obtained by maximizing the conditional probability density function (pdf) of the output samples given its past values, which is:

$$f(\mathbf{y}[1],\ldots,\mathbf{y}[N]/\mathbf{u}[1],\ldots,\mathbf{u}[N];\mathbf{R},\mathbf{A}) = \frac{1}{(2\pi)^{LN/2}|\mathbf{R}|^{N/2}}\prod_{n=1}^{N}\exp\{-\tfrac{1}{2}(\mathbf{y}[n]-\mathbf{A}\mathbf{u}[n])^T\mathbf{R}^{-1}(\mathbf{y}[n]-\mathbf{A}\mathbf{u}[n])\}$$

The log-likelihood function can be maximized by equaling its derivations with respect to **R** and **A**, and solving two matrix equations. This process yields:

$$\hat{\mathbf{A}}_{ML} = \left(\sum_{n=1}^{N}\mathbf{y}[n]\mathbf{u}^T[n]\right)\left(\sum_{n=1}^{N}\mathbf{u}[n]\mathbf{u}^T[n]\right)^{-1} \qquad \hat{\mathbf{R}}_{ML} = \frac{1}{N}\sum_{n=1}^{N}\mathbf{y}[n]\mathbf{y}^T[n] - \hat{\mathbf{A}}_{ML}\frac{1}{N}\sum_{n=1}^{N}\mathbf{u}[n]\mathbf{y}^T[n]$$

We then examine the eigenvalues of the matrix **R**. This is a full rank matrix; therefore it has L non-zero eigenvalues. According to this, given sufficient high SNR, the two highest K eigenvalues are related to the signal, while the other L-K eigenvalues represents the noise level.

The decision on which eigenvalues should be related to the signal, such as the decision about the AR order model, M, can be done using model order selection criteria, such as MDL and AIC. In order to quantify the probability of detection of OLI cases using the suggested method, we model the value of the second highest eigenvalue of the experiments into normal distribution of different mean and variance for One-Lung and of Two-Lung ventilation cases.

The invention in general involves the following:

1. An array of sensors placed on the patient's body in locations and spacing dictated by the state of the patient. The attachment of the sensors to the skin is performed in a convenient way.

2. An algorithm that enables the analysis of sounds generated by each lung and sounds generated by interfering signals. The algorithms allow the estimation of the state of ventilation and the early detection of OLI cases.

In conclusion we present a new device, already in prototype, which detects OLI in various clinical scenarios with a very high degree of accuracy. Further work is now being done in order to bring this device to a commercial stage.